SPECTROSCOPIC, COMPUTATIONAL, DOCKING AND CYTOTOXICITY INVESTIGATIONS ON SELECTED BENZIMIDAZOLE DERIVATIVES AS ANTI-BREAST CANCER AGENTS

A SYNOPSIS

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1. INTRODUCTION

One of the most common types of cancer among women worldwide is breast cancer. New therapeutic drugs with greater efficacy and fewer adverse effects are still needed, despite medical improvements. Current treatments include hormone therapy, chemotherapy, and targeted medicines are frequently constrained by patient efficacy, toxicity and drug resistance. The heterocyclic molecule benzoimidazole is well-known for its wide spectrum of biological actions, which include antibacterial, antiviral, anti-inflammatory, and anticancer qualities [1]. Its fundamental structure's capacity to interact with biological targets, specifically in the control of cellular proliferation and death, has demonstrated promise in the creation of novel anticancer medications [2]. According to earlier research, benzimidazole core alterations can greatly increase the compound's anticancer potential, which is why medication development is focusing on it. The identification and confirmation of the structure of novel benzimidazole derivatives depend heavily on spectroscopic methods (such as Raman, IR, and UV-Vis). Understanding their biological activity requires knowledge of their molecular interactions, functional groups and chemical environment, all of which are revealed by these methods [3].

Furthermore, there has been significant progress in the computational tools for quantum mechanical (QM) interpretation of frequency assignments. In the scaled quantum mechanical (SQM) approach, a scale factor in chemically related molecules corrects the estimated values' systematic errors [4]. Density functional theory (DFT) has been a viable QM technique in recent years. It is capable and comprehensive enough to be applied in pharmaceutical research. Due to its effectiveness and precision in assessing various molecular characteristics, DFT analysis has been recognized as a popular post-Hartree Fock (HF) technique for determining molecular energies, vibrational wave numbers and chemical structure [5]. The GAUSSIAN 09W program, which is being used to apply DFT theory, offers a versatile and potent toolkit for theoretical modelling [6]. For structural analysis in DFT techniques, Becke's three-parameter hybrid function linked to the Lee-Yang-Parr relationship (B3LYP) anticipates accurate computation and enhances the theory of electron correlation [7,8]. Hence, the B3LYP/6-311++G(d,p) basis set has been used in this investigation [9]. Moreover, drug development has employed molecular docking (MD) to provide potential protein-ligand interactions [10]. Consequently, the present

study has used both experimental and quantum computational processing to study the chosen benzimidazole derivatives.

2. LITERATURE REVIEW

The reviews of literature for the selected benzimidazole derivatives in this study are detailed as follows:

2.1. 6-Bromobenzimidazole (6BBZ)

The rings of benzene and imidazole have joined to form benzimidazoles, which are heteroatomic molecules. Numerous pharmacokinetic and pharmacodynamic properties are present in them. Salahuddin *et al.* [11] looked at how the benzimidazole nucleus is a useful tool in drug discovery because of its major pharmacophore and variety of biological roles. The molecular structure of benzimidazole derivatives using spectroscopy and DFT computation have been studied by Mohi *et al.* [12] and Anastassova *et al.* [13]. Additionally, Nguyen *et al.* [14], Ibrahim *et al.* [15], and Swathantraiah *et al.* [16] have investigated the effectiveness of benzimidazole derivatives against cancer cells. According to a thorough survey of the literature, the 6BBZ molecule has not yet been the focus of significant experimental and theoretical research. Therefore, using the DFT/B3LYP/6-311++G(d,p) basis set, the structural, vibrational wavenumbers, electronic and chemical properties of 6BBZ have been studied. Better clinical diagnoses are made possible by the binding energies from the MD studies and the cytotoxicity results of 6BBZ, which are demonstrated to be more effective against anti-cancer.

2.2. 5-Chlorobenzimidazole (5CBZ)

According to research by Kucuk [17], benzoimidazole's imidazole ring has two N atoms, which facilitates rapid transfer from one N atom to the other N atom. The H atom has two tautomer positions. According to a study by Sharma *et al.* [18], benzimidazole and its derivatives are natural forms of Vitamin B12. Their biological properties, as analyzed by Ebenezer *et al.* [19], make them a prominent structure in medicinal chemistry and are frequently employed in pharmacology. Singh *et al*. [20] and Nath *et al*. [21] have found that compounds containing benzimidazole substitutions have antibacterial, antifungal, anti-inflammatory, antiviral, and anticancer activities. In particular, benzimidazole derivatives have drawn more attention as potential cancer therapies. The pharmacological sector can produce medications with significant therapeutic promise since they exhibit a range of oxidation states and interact with a number of negative chemicals. Song *et al*. [22] and

Lee *et al*. [23] have conducted numerous investigations into the effectiveness of benzimidazole derivatives against cancer cells. Hence, the DFT/B3LYP/6-311++G(d,p) approach was used in this investigation to calculate the structural, vibrational and electronic excited states associated with stability and reactivity of 5CBZ. Docking and cytotoxicity studies were carried out to further demonstrate 5CBZ's repressive function against proteins connected to breast cancer.

2.3. 5-Chloro-2-mercaptobenzimidazole (CMBZ)

Biologically active imidazole derivatives are essential for many biochemical reactions. As a result, imidazole fragments are utilized as building blocks while developing novel medications. According to Thomas *et al.* [24], imidazole compounds are found in a variety of antibacterial, antiprotozoal, antifungal, antihypertensive, and anticancer drugs. Additionally, according to Kucuk *et al*. [25], imidazole derivatives are extensively employed in coordination complexes, asymmetric catalysis, and organometallic chemistry. According to a careful review of the literature, the CMBZ molecule has not yet been the focus of extensive DFT or experimental research. As a result, the optimal structure of CMBZ has been studied in this work, potentially leading to a breakthrough in the creation of drugs based on molecular docking and cytotoxicity investigations. The different amino acid residues and ligand CMBZ have been analysed in terms of their binding affinities and other associated interactions.

2.4. 2-(2-Chlorophenyl)benzimidazole (CPBZ)

Benzimidazole derivatives are stronger, more beneficial molecules for medicine, and have a wide range of biochemicals since they include two nitrogens as heteroatoms. According to Farmanzadeh *et al.* [26] and Jian-Song *et al.* [27], coordination, ion-dipole, cation-stacking, hydrogen bonding, van der Waals force, and hydrophobic effect are some of the non-covalent interactions that can enable the special benzene-fused imidazole ring to rapidly link with a range of active targets in biological systems. Using the DFT Approach, Palani Murugan *et al.* [28] investigated the docking, spectroscopy, NBO and structural analysis for 5-nitrobenzimidazole. A thorough review of the literature shows that CPBZ has not yet been the subject of a comprehensive theoretical or experimental inquiry. Hence, the structural, vibrational wavenumber, and electrical characteristics of CPBZ have been computed using the DFT/B3LYP/6-311++G(d,p) basis set. To further establish the molecule’s repressive

role against proteins linked to breast cancer, docking and cytotoxicity research were conducted.

2.5. 2-(2-Bromophenyl)benzimidazole (BPBZ)

According to Slassi *et al*. [29] and Kumar *et al.* [30], all members of the benzimidazole family of heterocyclic aromatic compounds share the fundamental structural characteristic of linking a benzene molecule with a five-membered imidazole moiety. According to research by Bouchekioua *et al.* [31], molecules based on benzimidazoles are essential to medicinal chemistry because of their many pharmacological properties. A notable example of a heterocyclic organic compound that bears structural resemblance to human nucleotides is benzimidazole, an essential pharmacophore in pharmaceutical science. The phenyl benzimidazole derivatives have been the subject of spectroscopic and docking experiments previously reported by Fasiuddin *et al.* [32]. However, a comprehensive examination of the literature indicates that BPBZ has not yet been the focus of significant experimental and theoretical investigation. Hence, the intermolecular interactions, Mullikan charges, border orbital energies and the molecule's nucleophilic and electrophilic regions have all been calculated for BPBZ. Studies on docking and cytotoxicity were conducted to further illustrate the ligand BPBZ's ability to suppress proteins linked to breast cancer.

3. OBJECTIVES

Pharmaceutical and biological active benzimidazole derivatives are bought from a chemical firm. The FT-IR, FT-Raman and UV-Vis spectral measurements were taken using these samples. The purpose of vibrational spectroscopy is to validate the functional groups of molecules and to interpret molecular vibrations. The GAUSSIAN 09W program is used to perform the computational studies, including minimum energy, molecular geometry optimizations, thermodynamical properties, vibrational frequency calculations, IR intensity, Raman activity and force field calculations. It capitalizes on the B3LYP functional in conjunction with the standard 6-311++G(d,p) basis set. The other molecular characteristics, including the highest occupied and lowest unoccupied molecular orbitals (HOMO-LUMO), were first optimized, followed by the molecular structures [33]. The Molecular electrostatic potential (MEP) [34], Mulliken charge (MC) [35], Ultraviolet visible (UV-vis) [36] spectroscopic studies, Natural bond orbital (NBO) [37], Fukui function [38] and Density of states (DOS) [39] spectral analysis have been calculated. Greater assertion between the experimental and DFT calculated values are guaranteed by the SQM

approach. For distinguishing vibrational modes, the potential energy distribution (PED) is calculated using the VEDA 4.0 program [40] and Sundius's MOLVIB Program (Adaptation V7.0-G77) [41]. The MD method is a computer software tool that is beneficial for advanced pharmaceutical research and the identification of novel drugs. Protein information was obtained from the Protein Information Bank (http://www.pdb.org) [42]. Since the compounds were ligands, the accessible ligand databases were used to obtain their structures: http://pubchem.ncbi.nlm.nih.gov is the pubchem website [43]. By docking interactions with the molecules, the Discovery Studio (Adaptation: 2017 R2 client) [44] tool has been used to evaluate the location of amino acids and the structure of proteins. MD is the work of Auto Dock Vina software tool [45]. To assess a molecule's anti-cancer properties, in vitro cytotoxicity analysis has been employed [46]. Using the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)-SAR prediction method [47], the systems' toxicity has been evaluated. The aforementioned characteristics of the chosen compounds can be applied to a number of medicinal tasks.

4. RESEARCH PROBLEM

Even though benzimidazole derivatives have made great steps in their development as therapeutic potential in the field of pharmacology, a thorough integration of various research methodologies is still lacking in order to completely comprehend their therapeutic potential against breast cancer. Further, it's unclear how their chemical makeup and biological action relate to one another. This discrepancy could make it more difficult to optimize these substances for increased effectiveness and decreased toxicity. Consequently, further research is required to determine how minute structural modifications impact toxicity, bioavailability, and binding affinity. Many anti-cancer drugs may not be selective enough for cancer cells, which might result in toxicity and off-target effects. Therefore, to reduce side effects, research should concentrate on making these molecules more selective for malignant cells than healthy cells. To create safe treatments, in-depth research on the long-term impacts and safety profile of these substances in a biological setting is thus required. Further, the efficacy of benimidazole derivatives as medications may be limited by issues with solubility, stability, or bioavailability. To guarantee that these molecules can effectively reach the target tissues at therapeutic dosages, further study is needed to improve their pharmacokinetic characteristics, including efficient delivery methods. Also, the potential for benzimidazole derivatives to increase the effectiveness of other

anti-cancer treatments may not have been thoroughly investigated. Therefore, examining synergies with current treatments (such as immunotherapy, radiotherapy, and chemotherapy) may uncover more potent therapeutic approaches. Researchers would be able to go from early discoveries to more reliable, clinically viable treatments if these gaps were filled.

5. ORGANIZATION OF THESIS

The thesis comprises of **EIGHT** chapters

Chapter 1

In chapter 1, the theory of vibrational spectroscopy is covered, along with a synopsis of scaled quantum mechanical calculations and their latest developments. The topics covered in chapter one include spectrum recording, IR, Raman and UV-Vis spectrophotometer instrumentation and sample handling procedures.

Chapter 2

In chapter two, the reviews of literature for the selected biomolecules in this study are detailed.

Chapter 3

In chapter 3, the potential of 6-bromobenzimidazole (6BBZ) as an anti-breast cancer medication is investigated using spectroscopic, computational, cytotoxic, and docking approaches. The molecular vibrations and absorption were thoroughly revealed by spectroscopic techniques such as FTIR, Raman and UV-Vis studies. The molecular structure, energy gap and electronic distributions were evaluated using the B3LYP/6-311++G(d,p) method. With an IC_{50} value of 17.23 μg/mL, cytotoxicity assays showed that 6BBZ is efficient against MCF-7 breast cancer cells, while computational docking showed that it has a good binding affinity against proteins linked to breast cancer, particularly estrogen sulfotransferase. ADMET predictions imply that 6BBZ may be a powerful treatment option and all are detailed in chapter 3.

Chapter 4

In the chapter 4, the work is focussed on 5-chlorobenzimidazole (5CBZ) and investigated as a possible anti-breast cancer agent using both computational and experimental methodologies. FT-Raman, FTIR, and UV-Vis spectra were among the spectroscopic analyses. DFT computations were used to optimize the molecular geometry and to assign vibrational frequencies. The HOMO-LUMO, MEP, Mulliken, DOS, NBO and Fukui function analysis were carried out to examine the electronic characteristics. According to docking studies, 5CBZ has the potential to be used

therapeutically because of its great binding affinities with proteins linked to breast cancer. With an IC_{50} value of 16.82 µg/mL, cytotoxicity experiments on MCF-7 breast cancer cells also showed a significant inhibitory impact, proving its effectiveness. Its potential as a therapeutic treatment for breast cancer was highlighted by ADMET results. All of the aforementioned is covered in depth in chapter 4.

Chapter 5

In this chapter 5, the study uses both computational and experimental techniques to examine 5-chloro-2-mercaptobenzimidazole's (CMBZ) ability to prevent breast cancer. In order to optimize molecular geometry and assess vibrational frequencies, it makes use of spectroscopic techniques (FTIR, FT-Raman, UV-Vis) and DFT computation. The study emphasizes the electronic characteristics of the molecule, including HOMO-LUMO, MEP, Mulliken, DOS, NBO and Fukui function analysis. Strong binding with proteins linked to breast cancer is revealed by docking studies, and cytotoxicity experiments demonstrate that CMBZ efficiently inhibits the MCF-7 cell line with an IC_{50} value of 16.54 µg/mL. Furthermore, ADMET projections show good pharmacokinetics, confirming CMBZ's status as a viable treatment option for breast cancer. All the above are detailed in chapter 5.

Chapter 6

The investigation of 2-(2-Chlorophenyl)benzimidazole (CPBZ) as a possible anti-breast cancer drug is the main emphasis of this chapter. It combines computational approaches based on DFT with spectroscopic analysis using FT-IR, FT-Raman and UV-Vis techniques. The molecule's electronic properties, such as HOMO-LUMO, MEP, Mulliken, DOS, NBO and Fukui function analysis are highlighted. The molecule's promise as a therapy for breast cancer is demonstrated by molecular docking tests conducted against significant cancer proteins. The biological activities of CPBZ, particularly its cytotoxic effects on breast cancer cells, are also evaluated. ADMET projections assess the pharmacokinetics of CPBZ. Everything mentioned above is covered in chapter 6.

Chapter 7

In chapter 7, the quantum chemical studies of 2-(2-Bromophenyl)-1H-benzimidazole (BPBZ) is thoroughly examined. For experimental validation, it uses a variety of spectroscopic techniques (FTIR, FT-Raman, UV-Vis) to determine its vibrational and electronic properties. BPBZ interacts with proteins that are known to be associated with breast cancer, including the human progesterone receptor (1A28 -

Figure 1(a)), epidermal growth factor receptor (1M17 - Figure 1(b)), human estrogen receptor (1ERE- Figure 1(c)), and estrogen sulfotransferase receptor (1AQU - Figure 1(d)). The Figure 2(a) depicts the morphological changes and Figure 2(b) represents the % of cell survival in breast cancer MCF-7 cells after being treated with various dosages of BPBZ. BPBZ's pharmacokinetic appropriateness as a possible treatment for breast cancer is further supported by the ADMET predictions.

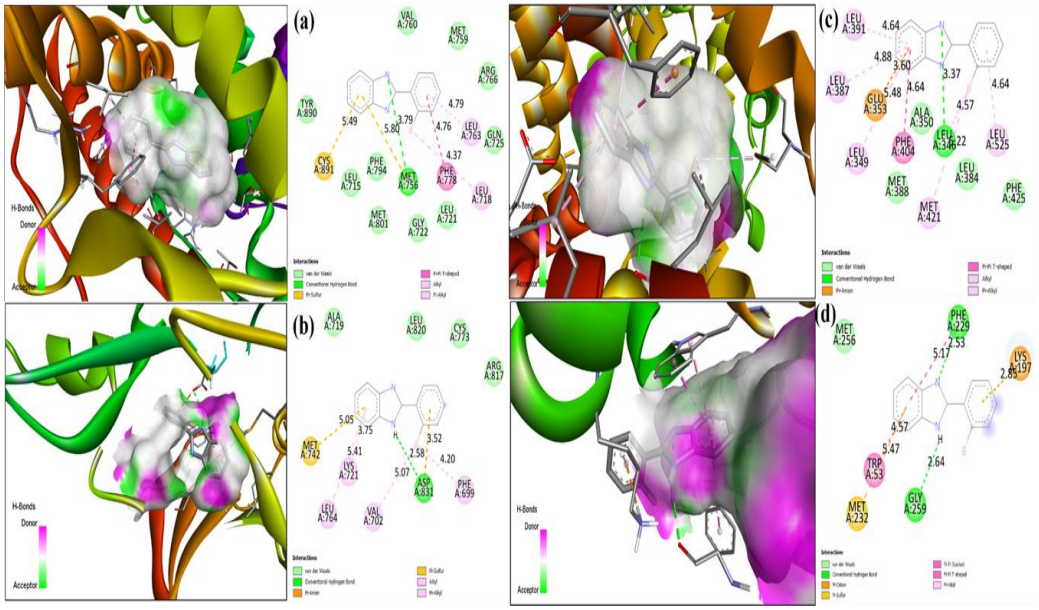

Figure 1: Interaction of 2-(2-Bromophenyl)-1H-benzimidazole with (a) 1A28 (b) 1M17 (c) 1ERE and (d) 1AQU

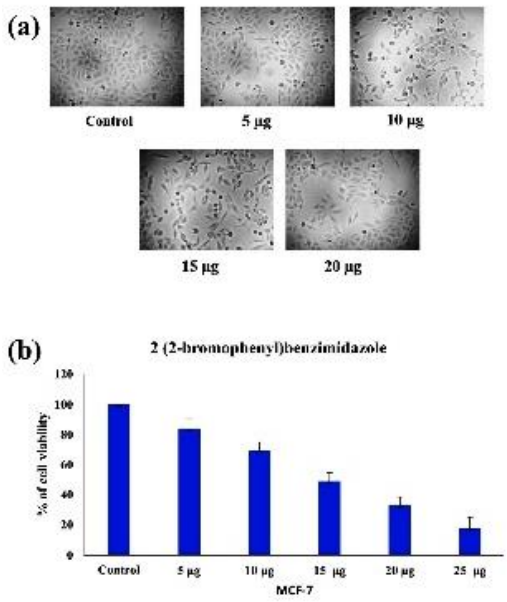

Figure 2: (a) Morphological changes (b) % of cell viability for different concentrations of 2-(2-Bromophenyl)-1H-benzimidazole against breast cancer MCF-7 cells

Chapter 8 Conclusion

In this chapter, the chosen compounds' bioactive capabilities are compared based on HOMO-LUMO, MEP, Mulliken, DOS, NBO, and Fukui function analysis. According to a methodical comparison of theoretical and experimental data, the scaled DFT functional approach is the most promising for obtaining accurate vibrational wavenumbers. The binding interactions of chosen chemicals with breast cancer proteins are compared by their docking results. The chosen compounds will be appropriate for medicinal uses with minimal adverse effects, according to cytotoxicity and ADMET standards. These findings will be helpful to researchers in the design and production of new anti-cancer drugs, as well as in the biochemical, pharmaceutical, electro-optical, and many other industries. All of the aforementioned is concluded in chapter 8.

6. REFERENCES

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